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REMARKS/ARGUMENTS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of three months of the period for response to the Office Action. The enclosed cheque includes the prescribed fee.

The Examiner stated there should be reference to US 09/210,995 to establish priority under 35 USC 120. By a Preliminary Amendment, a reference was added to page 1 to the effect that the application is a National Phase application under 35 USC 371 of PCT/CA99/01189. This reference now has been modified to recite the filing date of the PCT filing and that the PCT application is a continuation of copending Application No. 09/210,995.

The applicants are not aware of any changes required to be made to the specification to correct errors therein.

The Examiner indicated that the recitation of incorporation of material by reference to copending applications is improper, on the basis that the applications do not appear to have been published. In this regard, the PCT publications corresponding to the pending United States patent applications are specified (newly added by this Amendment, with respect to USAN 09/167,568). The technical content of the US patent applications then has been published.

The Examiner objected to the abbreviation "USAN" on page 6. This abbreviation stands for United States Application Number. It replaces the previously "USSN" abbreviation, since US patent applications are no longer referred to as having a serial number but rather an application number. Accordingly, no correction is required.

The Examiner noted that the application does not contain an Abstract but that the abstract from the International Application will be used in this filing.

The Examiner noted that use of trademarks should be capitialized whenever it appears and be accompanied by generic terminology. The adjuvants

identified by trademarks on pages 5 and 6 have been acknowledged as such and generic terminology added.

The Examiner rejected claims 1 to 26 under 35 USC 112, first paragraph, on the basis that the specification, while enabling for immunogenic compositions comprising the analog H91A Hin47 having decreased protease activity and a recombinant high molecular weight (rHMW) protein to confer protection against *Haemophilus influenzae*, does not reasonably provide enablement for an immunogenic composition comprising at least two different antigens of *Haemophilus influenzae* where at least one is an adhesin and the other is not an adhesin. Accordingly, the Examiner is of the view that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Reconsideration is requested.

It is noted that new claim 27 has been added, directed to the combination of subject matter which the Examiner indicates is enabled. Accordingly, irrespective of the remaining claims, it is submitted that claim 27 is fully enabled and not subject to rejection under 35 USC 112, first paragraph.

However, it is submitted that the enablement extends beyond the narrow confines of claim 27. The application relates to an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae*, comprising at least two different antigens of *Haemophilus influenzae*. At least one of the antigens is an adhesin and the other of the antigens is not an adhesin.

The antigen which is an adhesin may be a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae* (claim 2), which, according to page 4, line 22, may be produced recombinantly. According to page 3, lines 12 to 13, the corresponding naturally-occurring proteins also may be employed.

The antigen which is not an adhesin may be a non-proteolytic heat shock protein of a strain of *Haemophilus influenzae* (claim 4), specifically an analog

of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than 10% of that of natural Hin47 protein (claim 5).

The HMW proteins are described in Barenkamp et al cited by the Examiner in the prior art rejection while the Hin47 analogs are described in the Loosmore et al reference cited by the Examiner in the prior art rejection. In the Barenkamp et al reference, there is described both the isolation of the HMW protein from natural-source materials and recombinant production. There is no reason to suppose that the proteins produced recombinantly or from natural-source material would function significantly differently. It is submitted, therefore, that the enablement is not limited to recombinantly-produced HMW protein.

In the Loosmore et al reference, there is described the manner of producing the non-proteolytic analog of Hin47 protein. In this respect, at least one amino acid contributing to protease activity is deleted or replaced by a different amino acid. The Loosmore et al reference describes how to identify such amino acid by comparison to known proteases. The reference specifically describes that the deleted or replaced amino acid may be selected from amino acids 195 to 201 and specifically describes replacement of Serine-197 with alanine. Another specific amino acid mutation described is Histidine-91 replaced with alanine, lysine or arginine-121 to alanine. The immunogenic properties of these various mutants is described in Loosmore et al.

Based on this information, there is no reason to suppose that any non-proteolytic analog would function in the same manner as the specific H91A Hin47 analog utilized in the experiments described in the application. It is submitted that enablement is not limited to the specific H91A Hin47 analog, but rather extends at least to any non-proteolytic analog of the Hin47 protein.

The Examiner indicates that the objection of lack of enablement is based, to some extent, upon lack of guidance as to how to determine compositions other than that specifically identified by the Examiner. It is submitted that such is not the case.

Specifically, the specification tells a person skilled in the art that two different antigens of *Haemophilus influenzae* are employed and that one of them has to be an adhesin and the other does not. Testing to determine if an antigen is an adhesin or not an adhesin is within the skill of the art. In this regard, the Examiner's attention is directed to the experimentation described in Barenkamp.

In addition, the person skilled in the art is advised that one such adhesin protein is the HMW protein, where that is described and how to produce it both from natural-source materials and recombinantly (see page 2, line 23 to page 3, line 23). In addition, the person skilled in the art is advised that one such non-adhesin protein is a non-proteolytic analog of Hin47 protein or other non-proteolytic heat shock protein and how to produce such an analog (see page 3, line 14 to page 3 line 31).

Having regard to the foregoing discussion, it is submitted that claims 1 to 26, insofar as they remain in the application, are fully enabled by the disclosure and hence the rejection thereof under 35 USC 112, first paragraph, should be withdrawn.

The Examiner rejected claim 26 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Claim 26 has been deleted, thereby rendering the rejection moot.

The Examiner rejected claim 26 under 35 USC 101 on the basis that the claimed invention is not a proper process claim under 35 USC 101. As noted above, claim 26 has been deleted, thereby obviating the rejection.

The Examiner rejected claims 1 to 22 and 24 to 26 under 35 USC 103(a) as being unpatentable over Barenkamp (WO 97/36914) in view of Loosmore et al (USP 5,06,139). Of these claims, claims 1 to 5 and 25, are pending, claim 27 has been newly added. Reconsideration is requested.

Claim 1 defines an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae* comprising at least two different antigens of *Haemophilus influenzae*.

- one of which antigens is an adhesin
- the other of which antigens is not an adhesin

The Examiner has identified Barenkamp et al as describing a *Haemophilus influenzae* protein which is an adhesin and Loosmore as describing a *Haemophilus influenzae* protein which is not an adhesin. The applicants position is that neither reference provides the motivation to combine the two immunogens in a single composition, as required by claim 1.

As the Examiner points out, both references contain the statement:

> "The immunogenic composition of the invention may further comprise at least one other immunogenic or immunostimulating material" (Barenkamp, p. 7, ll 1 to 5; Loosmore, col. 3, ll 63 to 65).

The only "immunogenic or immunostimulating material" identified is an adjuvant, suggesting that the latter materials are preferred additional components, rather than an immunogenic material. In any event, there is no immunogenic material particularly specified in either reference and neither does the Examiner suggest that there is.

The two references also contain the statement:

> "A vaccine which contains antigenic material of only one pathogen is a monovalent vaccine. Vaccines which contain antigenic material of several pathogens are combined vaccines and also belong to the present invention. Such combined vaccines contain, for example, material from various pathogens or from various strains of the same pathogen or from combinations of various pathogens" (p. 22, ll 1 to 8 of Barenkamp; col. 9, ll 14 to 19 of Loosmore).

While suggesting various combinations, there is no suggestion here to combine <u>different</u> proteins derived from the <u>same</u> pathogen, as in applicants claim 1. Again, the references are silent as to any specific combination contemplated.

(The presence of these same passages in the two references is not simply a coincidence, but rather the undersigned attorney wrote both cases).

The Examiner's view is best summarized by the statement in the Office Action that:

> "No more than routine skill was required at the time of appellants invention to combine two well-known compositions, i.e. two different antigens of *H. influenzae*, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for that very same purpose of providing an immunogenic composition."

However, the cited prior art lacks the motivation to do so. As noted above, there are vague, non-specified indications in both references to combine other components with the specific immunogen, but there is no specific indication as to what that other component may comprise, other than an adjuvant (first quotation above) or materials from the pathogens and/or materials from various strains of the same pathogen (second quotation above). There is no clear direction to combine an antigen of *Haemophilus influenzae* which is an adhesin with an antigen of *Haemophilus influenzae* which is not an adhesin, as required by claim 1.

As the Examiner has pointed out, on page 49, lines 15 to 19 of Barenkamp, it is stated:

> ".... the data suggests the HMW adhesin proteins are potentially important protective antigens which may comprise one component of a multi-component NTHI vaccine."

It is conceded that the passage suggests the possibility of combining the HMW adhesin proteins with other *Haemophilus* proteins. However, the passage appears to suggests that only *Haemophilus* proteins which are adhesins are appropriate components. There is no suggestion that an antigen of *Haemophilus influenzae* which is not an adhesin may be combined with an antigen of *Haemophilus influenzae* which is an adhesin, as required by claim 1. The non-proteolytic analog of Hin47 is <u>not</u> an adhesin (although initially thought to be adhesin, see col. 2, line 17 of Loosmore et al). (It is pointed out that the Examiner is incorrect in the statement

that the adhesin protein "should" comprises one component of the NTHI vaccine. As can be seen from the above quotation, Barenkamp uses the word "may").

Even if the Examiner finds motivation in this passage of Barenkamp to combine the HMW protein with another *Haemophilus* antigen, whether an adhesin or not, such motivation still provides no motivation to select the non-proteolytic Hin47 analog as the other *Haemophilus* antigen.

There have been a significant number of *Haemophilus* proteins identified as vaccine candidates besides the HMW and Hin47 analog proteins. These proteins include the various outer membrane proteins A to H, lactoferrin and transferrin receptor proteins and the P1, P2, P6 and D15 proteins. It is submitted that there is no motivation provided by the cited prior art why a person skilled in the art would specifically select, from all the optional possibilities, the non-proteolytic Hin47 analog to combine with the HMW protein.

Having regard to the above, it is submitted that claims 1 to 22 and 24 to 26, insofar as they remain in the application, are patentable over the applied prior art and hence the rejection of the claims under 35 USC 103(a) as being unpatentable over Barenkamp et al in view of Loosmore et al, should be withdrawn.

The Examiner rejected claim 23 under 35 USC 103(a) as being unpatentable over Barenkamp et al and Loosmore et al in view of Anilionis et al. Since claim 23 has been deleted, the rejection is obviated.

It is noted that the Examiner asserts:

> "Barenkamp et al teach complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine, hepatitis B virus antigen and others (page 24-25, lines 7-10)."

This is an incorrect statement. The references to herpes simplex virus vaccine and pseudorabies virus vaccine (page 24, ll. 19 to 21) are made in the context of reporting work done by Lockhoff (USP 4,855,283) using glycolipid analogs as adjuvants, suggesting that such analogs could be used in the HMW-based

composition as adjuvants. There is absolutely no suggestion in Barenkamp of "complexing additional components to the immunogenic composition" in the form of herpes simplex virus (HSV), as asserted by the Examiner, but rather the possibility to use prior art glycolipid analogs as an adjuvant for the HMW protein is discussed since they have previously been used with HSV.

The references to tetanus toxoid and poliomyelitis virus vaccine (page 24, ll. 28 to 30) are in the context of reporting work performed by Maloney (USP 4,258,029) using octadecyl tyrosine hydrochloride (OTH) as an adjuvant, suggesting that OTH could be used as an adjuvant in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining tetanus toxoid and/or polio vaccine with HMW in an immunogenic composition.

Similarly, the reference to hepatitis B virus antigen (page 24, ll. 31 to 32) is in the context of reporting work performed by Nixon-George et al (ref. 30) using octadecyl esters of aromatic amino acids as an adjuvant, suggesting that such material could be used as an adjuvant in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining hepatitis B virus antigen with HMW in an immunogenic composition.

The Examiner provisionally rejected claims 6 to 20 under 35 USC 101 as claiming the same invention as that of claims 6 to 24 of copending Application No. 09/210,995. As the Examiner notes, the rejection is a provisional one since the conflicting claims have not, in fact, been patented. Claims 6 to 24 have been deleted from the application, thereby obviating the rejection.

The Examiner provisionally rejected claims 1 to 5, 25 and 26 under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 6 to 24 of copending Application No. 09/210,995.

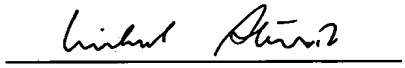
A rejection of obviousness-type double patenting, even if provisional, may be overcome by submitting a Terminal Disclaimer. Submitted herewith is a Terminal Disclaimer, disclaiming the term of the patent to be granted on this application which may extend beyond the term of the patent to be granted on

Application No. 09/210,995, signed by the attorney of record. The enclosed cheque includes the prescribed fee for a Terminal Disclaimer. It is submitted that the obviousness-type double patenting rejection thereby is overcome.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

On the insert to page 1, the paragraph has been rewritten as follows:

"This application is a national phase application under 35 U.S.C. 371 of PCT/CA99/01189 filed December 15, 1999, which is a continuation of copending US Patent Application No. 09/210,995 filed December 15, 1998."

Please replace the paragraph beginning at page 2, line 31, with the following rewritten paragraph:

"The production of native HMW proteins from *H. influenzae* strains is very low and a method for producing protective recombinant HMW (rHMW) proteins has been described in copending United States Patent Application No. 09/167,568 filed October 7, 1998, assigned to the assignee hereof and the disclosure of which is incorporated herein by reference (WO 00/20609). A chinchilla nasopharyngeal colonization model has been developed specifically to demonstrate vaccine efficacy of adhesins (ref. 14) and the rHMW proteins are protective in this model as described in the aforementioned copending United States Patent Application No. 09/167,568. The rHMW1A and rHMW2A proteins were shown to afford equivalent protection to each other and the rHMW1A protein was chosen for further vaccine studies. In this application, rHMW refers to the recombinant HMW1A protein from NTHi strain 12, although the corresponding recombinant HMW1A protein from other NTHi strains and the corresponding rHMW2A protein from NTHi strains may be employed for the rHMW. The corresponding naturally-occurring proteins also may be employed."

Please replace the paragraph beginning at page 5, line 23, with the following rewritten paragraph:

"The immunogenic composition of the invention may be further formulated with an adjuvant. Such adjuvant for use in the present invention may include (but not limited to) aluminum phosphate, aluminum hydroxide, [QS21] QS21 (trademark for a saponin adjuvant isolated from the bark of the Quillaja saponaria tree), [Quil A] QUIL A (trademark for a complex mixture of saponins from Quillaja saponaria and carbohydrates), derivatives and components thereof, ISCOM matrix, calcium phosphate, calcium hydroxide, zinc hydroxide, a glycolipid analog, an octadecyl ester of an amino acid, a muramyl dipeptide, polyphosphazene, [ISCOPREP] ISCOPREP (trademark for a purified form of saponins derived from Quillaja saponaria), [DC-chol] DC-CHOL (trademark of 3b-(N-(N',N'-dimethyl aminomethane)-carbamoyl) cholesterol, [DDBA] DDBA (trademark of dimethyldioctadecylammonium bromide) and a lipoprotein and other adjuvants, including bacterial toxins, components and derivatives thereof as described, for example, in USAN 08/258,228 filed June 10, 1994, assigned to the assignee hereof and the disclosure of which is incorporated herein by reference (WO 95/34323). Under particular circumstances, adjuvants that induce a Th1 response are desirable. Advantageous combinations of adjuvants are described in copending United States Patent Applications No. 08/261,194 filed June 16, 1994 and 08/483,856 filed June 7, 1995, assigned to the assignee hereof and the disclosures of which are incorporated herein by reference (WO 95/34308, published November 21, 1995). The adjuvant preferably may comprise aluminum phosphate or aluminum hydroxide (collectively known as alum)."

In the Claims:

Claims 6 to 24 and 26 have been cancelled.

Claim 25 has been amended as follows:

25. (Amended) A method of immunizing a host against disease caused by infection with *Haemophilus influenzae*, including otitis media, which comprises administering to the host an immunoeffective amount of a composition as claimed in claim 1 [or 6].

New claim 27 has been added as follows:

27. (New) The composition of claim 1 wherein said antigen which is an adhesin in a recombinantly-produced high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae* and said antigen which his not an adhesin is an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of that of natural Hin47 protein, in which Histidine-91 is replaced by alanine.